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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,143	EILERTSEN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *1-24 and 35-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 05/19/2004 has been entered. Claims 1-24 and 35-59 are withdrawn as being drawn to a non-elected invention. Claims 25-34 are pending and under current consideration.

Drawings

The color drawings submitted 03/12/2004 have been received. Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Specification

The disclosure is objected to because of the following informalities: The specification contains references to Tables (for example page 89, line 21; page 95, line

28). The specification contains descriptions of Tables 1 and 2 (page 47, lines 16-20). However, no tables have been identified in the disclosure.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 25-34 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record set forth on pages 3-9 of the office action mailed 10/06/2003. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 25-30 are directed to a method of identifying a developmentally competent cell line by comparing the expression pattern of a nuclear transfer embryo to a gene expression database wherein the comparison identifies the embryos resulting from nuclear transfer from a developmentally competent cell. Claims 31-34 are directed to methods of assessing the effect of changes in a nuclear transfer protocol by performing nuclear transfer according to two differing nuclear transfer protocols and determining the developmental competence of the each of the two embryonic cell populations by comparing the expression pattern of each nuclear transfer embryo to a gene expression database wherein the comparison identifies the embryos resulting from nuclear transfer

from a developmentally competent cell and assessing the effect of the change by comparing the developmental competence of each nuclear transfer embryo.

The specification describes identifying from embryos, ESTs that correlate with developmental competence. To identify the ESTs, microarray analysis of cDNAs derived from individual in vivo generated embryos and of an individual embryo generated by nuclear transfer using cell lines known to yield developmentally competent embryos was performed with comparison of each population of cDNAs and with cDNAs from embryos generated by nuclear transfer using cell lines known to not be capable of giving rise to developmentally competent embryos (pages 91-96). The specification describes identifying 13 cDNAs associated with two *in vivo* derived embryos and one nuclear transfer embryo derived from a cell line known to yield developmentally competent embryos. These 13 ESTs were not observed in two embryos derived from nuclear transfer using two cell lines known to not be developmentally competent and were also not observed in nuclear transfer embryos derived from a previously uncharacterized line that failed to give rise to developmentally competent embryos (page 96, lines 12-13). One cDNA was identified as being present in the three developmentally incompetent cell lines and absent from the in vivo embryos as well as the embryos derived by nuclear transfer from the known, developmentally competent cell lines (page 96, lines 13-14).

Applicant has argued that the concern that the specification fails to provide the sequences of the genes in the database that indicate developmental competence is misplaced (paragraph bridging pages 7-8). Applicant argued "What is important is to

identify sequences for the database that are known to be present and/or expressed in a cell line that had been demonstrated to be developmentally competent..."

In response, Applicant is not claiming a method of making a database of sequences known to be present and/or expressed in a developmentally competent cell line. Applicant is claiming a method of using that database without disclosing what the database is. The claims encompass any database. The skilled artisan must know what database to compare the gene expression profile of a nuclear transfer embryo to carry out the claimed methods.

Applicant has argued that the specification has provided copious instruction on how to identify differentially expressed nucleic acids (page 8, paragraph 2).

In response, the rejection is not on the grounds of how to compare, but is on the grounds of what to compare the genes expressed in the embryo to and what results will indicate developmental competence. Without knowing what results or gene expression profile indicates competence, the skilled artisan cannot carry out the claimed method.

Applicant argues that only a comparison of sequences need to be made and the sequences correlated to developmental competence or incompetence (page 8. paragraph 3).

In response, again, the claims are not to methods of correlating sequences to developmental competence but to identifying cell lines that are developmentally competent. Applicant's arguments relate to a method of identifying genes that correlate with developmental competence and not the claimed methods of identifying a developmentally competent cell line. With respect to applicant's remarks regarding the unclaimed subject matter of identifying genes correlating to developmental competence,

however, Applicant is directed to pages 5-7 of the previous office action outlining the state of the art as it relates to the methods disclosed in the specification. Briefly, the state of the art demonstrates that even when using a developmentally competent cell line, very few embryos actually develop. Therefore, if a small number of nuclear transfer embryos are made from any given cell line, and the embryos are sacrificed for gene expression comparison, one cannot know if those embryos themselves were developmentally competent and that their gene expression profile reflected developmental competence despite knowing that they were derived using nuclei from a developmentally competent cell line. The examples in the specification are drawn to comparing expression profiles of embryos of various origins and identifying various gene expression patterns. This is done, blindly without knowing what the developmental competence of each embryo actually is regardless of knowing whether the donor cell line itself is considered developmentally competent. Therefore, Applicant's disclosed methods of arriving at a gene expression database with which to compare other uncharacterized donor lines, which is not specified by the claims, falls short of providing genes that are actually indicative of developmental competence.

Applicant argues, with respect to the rejection on the grounds that the claims do not specifically recite that comparisons be standardized between species and developmental stage wherein the developmental stage is accurately adjusted to compensate for differences in temporal gene expression for in vitro fertilized, nuclear transfer and in vivo derived embryos, that the concern is misplaced. Applicant argues that the claimed methods can be used with any clonable mammalian species; as such comparisons are valid across species.

In response, while the methods are not enabled for the reasons presented above, they are further not enabled because, in the simplest sense, one cannot reliably compare the gene expression pattern of a developing rat to a database generated based on pig sequences and expect that the same genes would be expressed as an indicator of developmental competence. As set forth on pages 8-9 of the previous office action, cellular differentiation begins at different stages in different animal species, in vitro versus in vivo developed animals of the same species develop differently, and culture conditions affect nuclear reprogramming within the same species. Furthermore, gene expression profiles differ with any given stage of development within given specie. In fact, Applicant argues on page 10 with respect to the rejection under 102(b) that one embryo may have very high production of a particular gene (product) while another has a very low production of the same gene (product). Therefore, the claims should be limited to comparing embryos of like species at comparable stages if development.

Therefore, in light of the breadth of the claims, the lack of direction provided in the specification as to what genes indicate developmental competence of an embryo and the parameters necessary to assess developmental competence of an embryo, and the state of the art establishing that the rate of successful reprogramming and development of nuclear transfer embryos is extremely low, it would require one of skill in the art undue experimentation to determine how to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 25-34 under 35 U.S.C. 102(b) as being anticipated by De Sousa (1999, Cloning, Vol. 1, pages 63-69) is maintained for reasons of record set forth on page 10 of the previous office action.

Applicant argues that DeSousa fails to teach all of the limitations of the claims because DeSousa does not teach that the developmental competence of nuclear transfer embryos can be determined by comparing nucleic acids derived from the embryos to a gene expression database.

In response, DeSousa explicitly states that "characterization of these changes will be invaluable for the identification of suitable cell types to serve as nuclear donors for embryos reconstitution (see Abstract and page 68, col. 1, paragraph 2). Therefore, DeSousa not only taught the method steps as claimed but also taught that such comparisons will allow the identification of cell types to serve as nuclear donors to improve cloning efficiency, which is the same as identifying a developmentally competent nuclear donor cell line.

Applicant also argues that DeSousa used pools of embryos, which differs from the claimed invention where individual embryos are used. Applicant argues that pools of embryos would not be useful in the claimed methods because expression differences would be overlooked. In response, however, the pools are of like embryos made in the same fashion. Use of pools of embryos would average out random differences in gene expression, revealing commonalities between embryos made using different methods. Furthermore, as set forth in the previous office action, the claims as broadly written

encompass analysis of pooled embryos. The claims fail to recite that the nucleic acid from each embryo is maintained separately and not pooled.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

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